Translation

PCT Application
PCT/CN2005/000408

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT050629C	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CN2005/000408	International filing date (*day/month/year*) 29.MAR.2005(29.03.2005)	Priority date (*day/month/year*) 01.APR.2004(01.04.2004)

International Patent Classification (IPC) or national classification and IPC

IPC[7] C07K16/18 ,C12N15/13 ,15/63,15/70, A61K39/395,A61P35/00

Applicant

BEIJING ABT GENETIC ENGINEERING TECHNOLGY CO., LTD. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of five sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic _____), containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report

   ☐ Box No. II Priority

   ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   ☐ Box No. IV Lack of unity of invention

   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   ☐ Box No. VI Certain documents cited

   ☐ Box No. VII Certain defects in the international application

   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand 29.MAR.2005(29.03.2005)	Date of completion of this report 06.JUL.2005(06.07.2005)
Name and mailing address of the IPEA/CN The State Intellectual Property Office, the P.R.China, 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer WANG, Boli Telephone No. 86-10-62085225

Form PCT/IPEA/409 (cover sheet) (April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CN2005/000408

Box No. I Basis of the report

1. With regard to the language, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rules 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished

pages * _____ as amended (together with any statement)under Article 19

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☐ on paper

   ☒ in electronic form

   c. time of filing/furnishing

   ☐ contained in the international application as filed

   ☒ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment * on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

**If item 4 in Box No.I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement:

Novelty (N)	Claims	4-13,15-20	YES
	Claims	1-3,14	NO
Inventive step (IS)	Claims		YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

D1: ACTA BIOCHIMICA et BIOPHYSICA SINICA, Vol.35,No.6
D2: HYBRIDOMA, Vol.9, No.1
D3: CN,A,1380341

2.1 Novelty:

Claims 1-3 and 14 lack novelty under PCT Article 33(2) as being anticipated by document 1(from page 503 to page 510). The document discloses a recombinant multifunctional single-chain trispecific antibody (scTsAb), which contains anti-ovarian carcinoma(OC) svFv, FC interlinker, anti-human CD3 scFv, HSA interlinker and V_H domain of anti-human CD28 antibody in turn. In addition, the scTsAb has a c-myc tag in the C termination. The antibody was constructed and expressed in *E.coli* BL21 Star strain. In order to harvest the recombinant protein, the culture was induced at 30℃ for 4h with 0.4 mmol/L IPTG. Moreover, the document 3(from page 7 to page 19 of the description) describes a cyclic single-chain trispecific antibody against human tumor which also comprises parts as described in the claims 1-3 of the present invention.

2.2 Inventive step:

Claims 4-13 and 15-20 lack an inventive step under PCT Article 33(3) as being obvious over document 1 in combination with document 2.

A mouse-human chimeric antibody specific for human carcinoebryonic antigen(CEA) was produced by recombinnant DNA techniques in the document 2(from page 43 to page 48). The nucleotide sequences and deduced amino sequences of the V_H gene and V_L gene of the anti-CEA antibody was also showed. So it would be obvious to one of the ordinary skilled in the art was made to obtain a scTsAb of claims 4-5 and 8-9 containing anti-CEA svFv, FC interlinker, anti-human CD3 scFv, HAS interlinker and V_H domain of anti-human CD28 antibody on the basis of document 1 and document 2. The techniques and methods for use are routinely determined in the gene engineering arts and do not bring out unexpected effect. The DNA sequences of the claimed scTsAb could be deduced according to triple codes. An expression vector containing the nucleotide sequences coding for the scTsAb and a host cell containing the expression vector were described in the document 1,whererin the vector was pTRI or psTRI and the host cell was *E.coli* BL21 Star. Thus, it would be obvious to one of the ordinary skilled in the art to get an expression vector as claimed in claim 10 or 11 and a host cell as claimed in claim 12 or 13 without the need for an inventive concept.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of Box V(Citations and explanations):

The additional features of dependent claims 15-16 could not confer inventiveness on which they depend because the feature of claim 15 was disclosed in the document 1 and the feature of claim 16 was a conventional method for purify protein in the art.

Document 1 also demonstrated that the scTsAb could be used for elimination of disseminated tumor cells. Certainly, it is easy for the skilled person to produce pharmaceutical combination with known antibodies. Consequently, the claims 17-20 of the present invention don't meet the requirements of PCT Article 33(3) in respect of inventive step.

2.3 Utility:

Claims 1-20 meet the criteria set out in PCT Article 33(4). The claimed invention would have been expected to have industrial applicability in the pharmaceutical field, e.g., in the treatment of cancer.

专 利 合 作 条 约

PCT

专利性国际初步报告

（PCT 第II章）

（PCT 36 和细则 70）

申请人或代理人的档案号 PCT050629C	关于后续行为　　参见 PCT/IPEA/416 表	
国际申请号 PCT/CN2005/000408	国际申请日（日/月/年） 29.3 月 2005(29.03.2005)	优先权日（日/月/年） 01.4 月 2004(01.04.2004)
国际专利分类(IPC)或者国家分类和 IPC 两种分类 IPC[7]　C07K16/18 ,C12N15/13 ,15/63,15/70, A61K39/395,A61P35/00		
申请人 北京安波特基因工程技术有限公司 等		

1. 本报告是国际初步审查单位根据条约 35 做出的国际初步审查报告，并依照条约 36 将其传送给申请人。

2. 本报告共计 5 页，包括扉页。

3. ☐ 本报告还有附件，

   a. ☐ (传送给国际局和申请人)共计 _____页，包含

   ☐修改后的并且作为本报告基础的说明书修改页、权利要求书修改页和/或附图修改页，和/或对本国际初步审查单位所做出的更正页(见 PCT 细则 70.16 和行政规程 607)。

   ☐国际初步审查单位认为修改超出原始公开范围的取代页，参见第 I 栏第 4 项和补充栏。

   b. ☐ （传送给国际局）共计 (指明电子载体的类型和数量) _____，包含有在与序列表有关的补充栏中指明的电子形式的序列表和/或与其相关的表格。（行政规程 802）

4. 本报告包括关于下列各项的内容：

- I ☒ 报告的基础
- II ☐ 优先权
- III ☐ 不做出关于新颖性、创造性和工业实用性的意见
- IV ☐ 缺乏发明的单一性
- V ☒ 按条约 35(2)关于新颖性、创造性或工业实用性的理由；支持这种意见的引证和解释
- VI ☐ 引用的某些文件
- VII ☐ 国际申请中的某些缺陷
- VIII ☐ 对国际申请的某些意见

提交要求书的日期 29.3 月 2005(29.03.2005)	完成本报告的日期 06.7 月 2005(06.07.2005)
中华人民共和国国家知识产权局 IPEA/CN 中国北京市海淀区西土城路 6 号(100088) 传真号：(86-10)62019451	受权官员 汪波莉 电话号码 (86-10)62085225

专利性国际初步报告

国际申请号
PCT/CN2005/000408

I. 报告的基础

1. 关于语言，本报告将基于：

☒ 申请提出时使用的语言。

☐ 该申请的_____语言译文，提供该种语言的译文是

☐ 为了国际检索而提交的译文所使用的语言（细则 12.3 和 23.1（b））。

☐ 为了国际申请的公布而提交的译文所使用的语言（细则 12.4）。

☐ 为了国际初步审查而提交的译文所使用的语言（细则55.2和/或55.3）。

2. 关于国际申请中各个部分，本报告基于（申请人为答复受理局根据条约 14 所发通知而提交的替换页，在本报告中视为“原始提交”的文件，不作为本报告的附件）

☒ 原始提交的国际申请。

☐ 说明书，第_____页 原始提交的，
第_____页 _____初审单位收到的，
第_____页 _____初审单位收到的。

☐ 权利要求，第_____页，原始提交的，
第_____页，按条约 19 条修改的(附有说明)，
第_____页 _____初审单位收到的，
第_____页 _____初审单位收到的。

☐ 附图，第_____页，原始提交的。
第_____页*，_____初审单位收到的，
第_____页*，_____初审单位收到的。

☒ 序列表和/或相关表格——参见与序列表有关的补充栏。

3. 修改导致以下内容的删除：

☐ 说明书，第_____页

☐ 权利要求，第_____项

☐ 附图，第_____页，图_____

☐ 序列表（*具体说明*）_____

☐ 与序列表相关的表格（*具体说明*）_____

4. ☐ 由于本报告附件的(某些)修改，如下所列，被认为超出了原始公开的范围，如补充栏所示，因此本报告是按照没有修改的情况做出的(细则 70.2(c))。

☐ 说明书，第_____页

☐ 权利要求，第_____项

☐ 附图，第_____页，图_____

☐ 序列表（具体说明）_____

☐ 与序列表相关的表格（具体说明）_____

*如果第 4 项适用，一些或全部的文件页可能做出“被取代”标记。

专利性国际初步报告

国际申请号
PCT/CN2005/000408

关于序列表的补充栏

续第 I 栏第 2 项：

1 关于本国际申请中所公开的对所要求保护的发明必要的核苷酸和/或氨基酸的序列表，本国际初步审查的建立是根据：

a. 文件的类型

☒ 序列表

☐ 与序列表相关的表格

b. 文件的形式

☐ 纸件形式

☒ 电子形式

c. 提交的时间

☐ 包含在国际申请中

☒ 以电子形式与国际申请同时提交

☐ 为了检索和/或审查的目的提交给初审单位的

☐ 以修改*的形式由初审单位在_____ 收到

2.另外，在提交了不只一个版本或副本的序列表和/或与序列表相关的表格情况下，已经提交了关于后续或附加版本与原始提交的文件相同或没有超出原始提交文件范围的声明。

3.其它意见:

*如果第一栏第 4 项适用，形成报告基础的序列表和/或相关表格可能做出“废除”标记。

专利性国际初步报告

国际申请号
PCT/CN2005/000408

V. 按条约 35 (2)关于新颖性、创造性或工业实用性的意见；支持这种理由的引证和解释

1. 意见

新颖性(N)	权利要求	4-13,15-20	是
	权利要求	1-3,14	否
创造性(IS)	权利要求		是
	权利要求	1-20	否
工业实用性(IA)	权利要求	1-20	是
	权利要求		否

2. 引证和解释（细则 70.7）

对比文件 1：生物化学与生物物理学报，第 35 卷第 6 期
对比文件 2：Hybridoma，第 9 卷第 1 期
对比文件 3：CN, A, 1380341

2.1 关于新颖性：

权利要求 1—3 和 14 相对于对比文件 1（第 503-510 页）不具有 PCT 第 33（2）条规定的新颖性。该对比文件公开了一种重组多功能单链三特异抗体（scTsAb），它由抗人卵巢癌单链抗体，FC 连接肽，抗人 CD3 单链抗体，HSA 连接肽和抗人 CD28 抗体 V_H 结构域片段依次连接而成。该 scTsAb 的 C 末端具有从 c-myc 标签。构建的抗体在大肠杆菌 BL21 中表达。为了收获重组蛋白，培养物用 0.4mmol/L 的 IPTG 在 30℃诱导表达 4 小时。此外，对比文件 3(说明书第 7-19 页)描述了一种抗人类肿瘤的环形单链三特异抗体，它也含有本发明权利要求 1-3 所述的抗体部分。

2.2 关于创造性：

权利要求 4—13 和 15—20 相对于对比文件 1 和对比文件 2 的结合不具有 PCT 第 33（3）条规定的创造性。

对比文件 2 中（第 43-48 页）利用 DNA 重组技术生产了一种抗人癌胚抗原（CEA）的鼠源嵌和抗体。同时公开了该抗 CEA 单抗重链可变区和轻链可变区的核苷酸序列和推导的氨基酸序列。这样，对本领域技术人员来说，在对比文件 1 和 2 的基础上得到权利要求 4—5 和 8—9 中含有抗 CEA 的单链抗体，FC 连接肽，抗人 CD3 单链抗体，HSA 连接肽和抗人 CD28 抗体 V_H 结构域片段的单链三特异抗体是显而易见的。所用的技术和方法是基因工程领域常用的，不会产生预料不到的效果。要求保护的 scTsAb 的 DNA 序列可由三联体密码推导获得。对比文件 1 还描述了含有 scTsAb 核苷酸序列的表达载体和含有表达载体的宿主细胞，其中载体是 pTRI 或 psTRI，宿主细胞是大肠杆菌 BL21。因此，对本领域技术人员来说，得到权利要求 10 或 11 要求保护的表达载体以及权利要求 12 或 13 要求保护的宿主细胞是显而易见的，不需要付出创造性劳动。

（见补充栏）

补充栏

当前面的任何一栏地方不够时使用

续栏：接V栏（引证和解释）

从属权利要求 15－16 的附加技术特征不能给它们引用的权利要求带来创造性，因为权利要求 15 的附加技术特征在对比文件 1 中已经公开，权利要求 16 的附加技术特征是本领域纯化蛋白的常规技术手段。

对比文件 1 还证明了 scTsAb 用于消除弥散的肿瘤细胞。当然，本领域技术人员用已知抗体生产药物组合物是很容易的。因而，本发明权利要求 17－20 不符合 PCT 第 33（3）条关于创造性的规定。

2.3 关于实用性：

权利要求1－20符合PCT第33（4）条关于实用性的规定。本发明在工业上可用于制备药物组和物，例如治疗癌症。